

Gastroresistant tablets for alimentary, dietetic and therapeutic use

The present invention relates to gastro-resistant formulations, preferably tablets, for alimentary or dietary use, which are obtained by mixing the composition with fat in order to achieve a prolonged release of the active principles contained therein to the organism.

The preparation of the gastro-resistant formulations is usually carried out so as to allow the active principle to be released and absorbed in a more or less retarded manner at the intestine level; alternatively, the active principle may be released and absorbed only in part at the stomach level, thus allowing a second fraction of the active principle to be released and absorbed at the intestine level.

The known technique for preparing gastro-resistant formulations with retarded release is as follows:

- A) Gastro-resistant formulations: these are tablets lined with gastro-resistant films, such as, for example, ethylcellulose, cellulose acetophthalate, polyacrylates, gum lac, keratine; the lined tablets are then coated with sugar.
- B) Layered formulations: they are prepared in the same manner as the gastro-resistant sugar-coated pills, with regard to coating of the tablets; a sprinkling powder such as starch or talcum, in which an active principle is dispersed using a water-soluble product such as gum arabic, agar-agar etc. as the adhesive, is attached layerwise to the coated core, in such a manner that the outermost layer and not the inner tablet is dissolved in the stomach.
- C) Capsules containing retarding agents; they are sugar cores in which the active principle is dispersed, followed by application of a protective coating as in para. A);
- D) Tablets in which retarding agents are dispersed in such a way that part of the active principle is present in the gastro-resistant retarding agents and part is present in the water-dispersible tablet;
- E) Multi-layered tablets in which one or more layers contain dissolution-retarding powders, such as cellulose-derived gum lacs so that the layers have different solubilities.

In general, they are formulations whose retarding effect is based on the use of excipients and/or adjuvants foreign to the mammalian organism, in particular of humans, which formulations are intended to maximize the absorption of the active

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principle without taking into consideration the normal physiological digestive processes.

However, the use of such substances is usually not very desirable, in particular in the case of dietary formulations and/or in the case of food additives which are intended to achieve instead an absorption of the active principle according to a kinetic profile which is as close as possible to the normal human digestive processes.

The recourse to "natural" absorption profiles is anyway desirable, even in the case of therapeutic formulations, for example in all those classes of patients who would be harmed by administering them non-"physiological" excipients and/or adjuvants; obvious examples are pregnant women, very young children, allergic subjects, etc. Now, according to the subject-matter of the present invention, a novel formulation with retarded release has been found, said formulation allowing the active principles to be absorbed utilizing the physiological digestive activity, i.e. imitating what happens with food ingested in the usual manner.

The present invention relates to a formulation in tablet form for oral use, containing at least one active principle with a pharmaceutical, dietary or alimentary action in combination with at least one fat and/or phospholipid, as the vehicle, in an amount of between 5 and 30%, relative to the weight of the formulation; preferably, such fats and/or phospholipids are present in an amount of between 20 and 30%, relative to the weight of the formulation.

The fatty acids contained in the fats and phospholipids which can be used for the purposes of the present invention are normally selected from those containing hydrogenated and non-hydrogenated fatty acids, either of synthetic or natural origin, having a chain comprising between 3 and 20 carbon atoms, preferably between 14 and 18 carbon atoms, and mixtures thereof.

A non-limiting list of such acids comprises, for example, palmitic acid, stearic acid, myristic acid, lauric acid, caprylic acid, capric acid, etc.

From a practical point of view, the fats can normally be selected from among cocoa butter, hydrogenated palm oil, hydrogenated vegetable fats such as peanut butter, animal fats such as lard, butter, bacon fat separately or in a mixture thereof.

The phospholipids are instead preferably used as lecithins and, in particular, as soya lecithin. If desired, the abovementioned fats and phospholipids may also be

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used in combination with alkali metal salts and/or alkaline earth metal salts of fatty acids having a chain comprising between 3 and 20 carbon atoms, preferably between 14 and 18 carbon atoms, or mixtures thereof, the preferred salts being those of sodium, potassium and calcium.

As indicated above, the active principles which can be used for the purposes of the present invention may have both a therapeutic and a dietary or alimentary action. The active principles with a therapeutic action may be selected from among non-steroid anti-inflammatory drugs (NSAID) and steroid anti-inflammatory drugs, tranquilizers, sleeping pills, anti-hypertensive, anti-histaminic and anti-asthmatic drugs; non-steroid anti-inflammatory drugs in turn may be selected from among ibuprofen, naproxen, ketoprofen, indomethacin, acetylsalicylic acid, mefenamic acid, flufenamic acid, etc.; the active principles with a dietary action may be selected from the group consisting of lactic acid microorganisms, beer yeasts, either as such or containing living cells, vitamins, minerals, amino acids, vegetable extracts, and derivatives thereof.

In the formulation according to the present invention, the active principle or principles, which may be used as such or in the form of esters or physiologically acceptable salts, can be mixed directly with said at least one fat and/or phospholipid without the addition of any excipients and/or adjuvants; in this case, the active principle or principles make up 70-95% by weight, preferably 75-90% by weight, of the formulation.

Alternatively, the abovementioned active principles may be used in combination with customary excipients and/or adjuvants known in the art; in this case, they are normally present in amounts of between 1 and 50%, preferably between 10 and 40%, relative to the total weight of the formulation.

The excipients used for the tablet according to the present invention may be selected from the group consisting of starches, maltodextrin, microcrystalline cellulose, talcum-modified cellulose, calcium carbonate, milk proteins, calcium stearate, magnesium stearate, sodium stearate, soya proteins or suitable inert powders, PVP, precipitated silica and are present in an amount of 10-30% by weight, preferably 20-30% by weight, relative to the total weight of the formulation.

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In order to determine the release activity, over time, of an active principle contained in a formulation according to the present invention (the qualitative and quantitative composition of which is given in Example 1), the dissolution test described in Farmacopea Ufficiale Italiana (Official Italian Pharmacopeia) was carried out. The results of said test are shown in the table below.

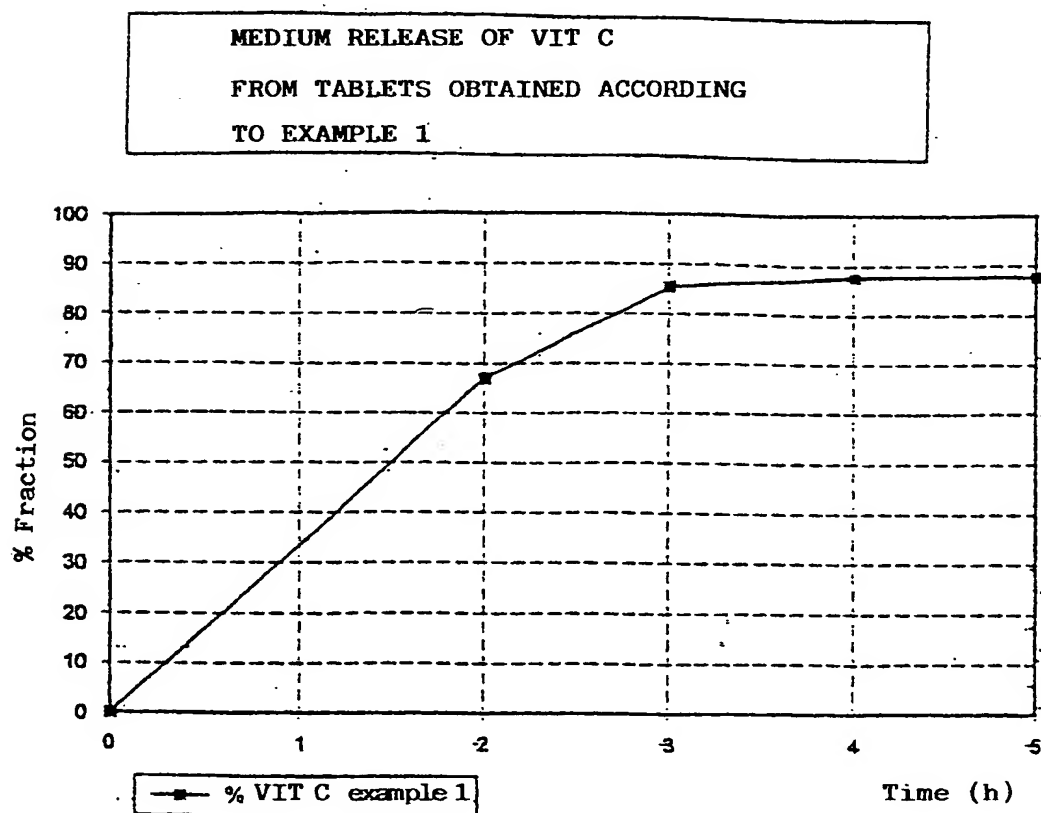


TABLE I

This dissolution test demonstrates the slow release, over time, of an active principle under physiological conditions which simulate the digestive processes which normally take place in the stomach.

The present invention is particularly suitable for the production of BIO-certified gastro-resistant tablets, provided that fats derived from biological cultivations and farms in accordance with current regulations are used.

The present invention furthermore relates to the process for the preparation of the formulations according to the present invention.

Said process comprises premixing an active principle as defined above in an amount of 1-50% by weight, relative to the total weight of the formulation, with the excipients as defined above, which in turn are present in an amount of 10-30%, relative to the total weight of the formulation. The mixture thus obtained by simple mixing at ambient temperature or by dry or wet granulation in accordance with the known technique is kneaded in a suitable kneader, usually a Z-type kneader or plunging-arm kneader, together with at least one fat and/or phospholipid in the melted state in an amount of between 5 and 30%, relative to the weight of the formulation.

The blend thus obtained is cooled to 5-20° C, preferably to 10°C-12° C, and then granulated, for example using an oscillating granulator of the Manesty type equipped with a perforated stainless steel plate having holes with a diameter of 1-4 mm, preferably 1-2 mm.

The granules thus obtained are compressed with a rotary tablet-compressing machine equipped with suitable punches. It is thus possible to obtain tablets of suitable weight.

In the case of tablets not containing added excipients and/or adjuvants, the active principle is mixed directly with the fat and/or phospholipid in the melted state; the mixture is then processed as described above.

In particular, the present invention is highly suitable for the preparation of layered tablets obtained with a suitable tablet-compressing machine such as, for example, a Manesty BB3B.

The process consists in compressing a layer obtained according to the prior art using one or more active principles mixed with known water-soluble or water-dispersible excipients and one layer obtained according to the present invention. If

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desired, it is also possible to use more than two layers with different degrees of solubility.

The examples which follow are given in order to describe better the present invention without, however, limiting its scope.

Example 1

1000 tablets are prepared, being formed by a fast-dissolving layer (Layer A) obtained by kneading, in a Z-type kneader, the following components together with 10% strength Klucel/water:

proline (100 g),

lysine (100 g),

cystine (100 g),

sodium carboxymethylcellulose (20 g)

The blend thus obtained is dried for 12 hours at 40°C in a drying cabinet, the resulting mixture is granulated in a Manesty granulator equipped with a perforated stainless steel plate having holes with a 2-mm diameter, giving a yield of 321.8 g.

The granules thus obtained are mixed in a rotating-screw mixer (SAGA) with :

red lake N° 40 all lake (0.25 g),

vitamin A 5,000,000 IU/g (800 µg/cpr +30%) (2.31 g),

vitamin E 50% SD (16 mg/cpr +20%) (12.8 g),

vitamin C granules (49.5 g),

magnesium stearate (5 g),

copper gluconate Cu 14% (1.2 mg/cpr + 5%) (6 g),

zinc gluconate Zn 13.4% (10 mg/cpr + 5%) (52.2 g)

selenium-containing yeast 2,000 µg/g (0.055 µg/cpr + 5%) (19 g)

glutathione on yeast (25 mg/cpr + 20%) (15 g),

rapidly disintegrating PVP (20 g),

potato starch (10 g),

silica gel (3 g),

maltodextrin (5 g),

microcrystalline cellulose (2 g),

water (0.5 g),

giving a total yield of 524.36 g.

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A second mixture is prepared and used to form the slow-dissolving layer (LAYER B) thus obtained:

lyophilized blueberry (15 g),
microcrystalline cellulose (50 g),
titanium dioxide (10 g),
nucleic acids (50 g),
blueberry extract 25% (50 g),
copper gluconate (1.5 g),
zinc gluconate (12.3 g),
copper gluconate (1.5 g),
zinc gluconate (13.8 g),
selenium-containing yeast (9.5 g),
glutathione on yeast (15 g),
vitamin A 500,000 IU/g (4.63 g),
vitamin E 50% SD (25.6 g),
vitamin C EC 97% (99 g),

All these components are mixed and kneaded in a Z-type kneader together with melted hydrogenated palm oil (50 g).

The blend obtained is cooled to 12°C and granulated in an oscillating granulator equipped with a stainless steel plate having holes with a 2 mm diameter, giving a total yield of 408 g.

The two mixtures thus obtained can be compressed with an oval punch using a double-layered tablet-compressing machine (MANESTY BB3B) producing oval tablets with a weight of 0.932 g, in which the first layer weighing 0.524 g is fast-dissolving and the second layer weighing 0.408 g is gastro-resistant and slow-dissolving.

Example 2

Example 1 is repeated, except that the following components are used:

Layer A (FAST-DISSOLVING)

folic acid 98% (0.3 mg/cpr + 20%) (0.12 g)
vitamin B6 33.1/3 (1.5 mg + 20%) (1.8 g)
beta carotene 20% (4mg/cpr + 10%) (7.4 g)
vitamin E 50% SD (116 mg/cpr) (12.8 g)

vitamin C EC 97 (120 mg/cpr +20%) (49.5 g)
copper gluconate Cu 14% (1.2 mg/cpr) (6 g)
zinc gluconate Zn 13.4% (10 mg/cpr) (52.3 g)
selenium-containing yeast 2000 µg/g (55 µg/cpr) (19.3 g)
lactose CD (150 g)

microcrystalline cellulose (30 g)

water (4 g)

potato starch (30 g)

rapidly disintegrating PVP (Kollidon CL) (10 g)

silicagel (10 g)

maltodextrin (8g)giving a total of 391.22 g:

Layer B (SLOW-DISSOLVING)

sulfomucopolysaccharides (25 g)

Gingko biloba (30 g)

copper gluconate Cu 14% (3 g)

zinc gluconate Zn 13.4% (26.2 g)

selenium-containing yeast 2,000 µg/g (9.7 g)

microcrystalline cellulose (50 g)

red iron oxide (5 g)

folic acid (0.24 g)

vitamin B6 33.1/3% (3.6 g)

vitamin E 50% (25.6 g)

vitamin C EC 97% (99 g)

beta carotene 20% (14.8 g)

melted hydrogenated palm oil (72 g)

silica gel (0.5%),

giving a total of 0.358 g.

Double-layered tablets weighing 0.749 g are prepared, the first layer of which weighing 0.391 g is fast-dissolving and the second one weighing 0.358 g is slow-dissolving.

The tablets can then be coated with a solution of
10 % strength Klucel/water.

Example 3

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the sum of the components (a), (b) and (c) making up 100% by weight of the formulation.

8. Formulation according to Claim 7, characterized in that said excipients are selected from among starches, maltodextrin, microcrystalline cellulose, talcum-modified cellulose, calcium carbonate, milk proteins, calcium stearate, magnesium stearate, sodium stearate, soya proteins or suitable inert powders, PVP, and precipitated silica.

9. Process for the preparation of a formulation according to Claim 5 in which:

- a) said at least one active principle is mixed with said at least one fat and/or phospholipid in the melted state in the weight proportions defined above;
- b) the blend thus obtained is cooled to 5-20°C, preferably to 10°C-12°C, and then granulated using a granulator having holes with a diameter of between 1 and 4 mm, preferably between 1 and 2 mm;
- c) the granules thus obtained are then compressed.

10. Process for the preparation of a formulation according to Claim 7 in which:

- d) said at least one active principle is premixed at ambient temperature with said excipients and/or adjuvants in the weight proportions defined above;
- e) the mixture thus obtained is mixed with said at least one fat and/or phospholipid in the melted state in the weight proportions defined above;
- f) the blend thus obtained is cooled to 5-20°C, preferably to 10°C-12°C, and then granulated using a granulator having holes with a diameter of between 1 and 4 mm, preferably between 1 and 2 mm;
- g) the granules thus obtained are then compressed.

2025-2026-2027-2028-2029-2030-2031-2032-2033-2034-2035-2036-2037-2038-2039-2040-2041-2042-2043-2044-2045-2046-2047-2048-2049-2050-2051-2052-2053-2054-2055-2056-2057-2058-2059-2060-2061-2062-2063-2064-2065-2066-2067-2068-2069-2070-2071-2072-2073-2074-2075-2076-2077-2078-2079-2080-2081-2082-2083-2084-2085-2086-2087-2088-2089-2090-2091-2092-2093-2094-2095-2096-2097-2098-2099-2100-2101-2102-2103-2104-2105-2106-2107-2108-2109-2110-2111-2112-2113-2114-2115-2116-2117-2118-2119-2120-2121-2122-2123-2124-2125-2126-2127-2128-2129-2130-2131-2132-2133-2134-2135-2136-2137-2138-2139-2140-2141-2142-2143-2144-2145-2146-2147-2148-2149-2150-2151-2152-2153-2154-2155-2156-2157-2158-2159-2160-2161-2162-2163-2164-2165-2166-2167-2168-2169-2170-2171-2172-2173-2174-2175-2176-2177-2178-2179-2180-2181-2182-2183-2184-2185-2186-2187-2188-2189-2190-2191-2192-2193-2194-2195-2196-2197-2198-2199-2200-2201-2202-2203-2204-2205-2206-2207-2208-2209-2210-2211-2212-2213-2214-2215-2216-2217-2218-2219-2220-2221-2222-2223-2224-2225-2226-2227-2228-2229-2230-2231-2232-2233-2234-2235-2236-2237-2238-2239-2240-2241-2242-2243-2244-2245-2246-2247-2248-2249-2250-2251-2252-2253-2254-2255-2256-2257-2258-2259-2260-2261-2262-2263-2264-2265-2266-2267-2268-2269-2270-2271-2272-2273-2274-2275-2276-2277-2278-2279-2280-2281-2282-2283-2284-2285-2286-2287-2288-2289-2290-2291-2292-2293-2294-2295-2296-2297-2298-2299-2300-2301-2302-2303-2304-2305-2306-2307-2308-2309-2310-2311-2312-2313-2314-2315-2316-2317-2318-2319-2320-2321-2322-2323-2324-2325-2326-2327-2328-2329-2330-2331-2332-2333-2334-2335-2336-2337-2338-2339-2340-2341-2342-2343-2344-2345-2346-2347-2348-2349-2350-2351-2352-2353-2354-2355-2356-2357-2358-2359-2360-2361-2362-2363-2364-2365-2366-2367-2368-2369-2370-2371-2372-2373-2374-2375-2376-2377-2378-2379-2380-2381-2382-2383-2384-2385-2386-2387-2388-2389-2390-2391-2392-2393-2394-2395-2396-2397-2398-2399-2400-2401-2402-2403-2404-2405-2406-2407-2408-2409-2410-2411-2412-2413-2414-2415-2416-2417-2418-2419-2420-2421-2422-2423-2424-2425-2426-2427-2428-2429-2430-2431-2432-2433-2434-2435-2436-2437-2438-2439-2440-2441-2442-2443-2444-2445-2446-2447-2448-2449-2450-2451-2452-2453-2454-2455-2456-2457-2458-2459-2460-2461-2462-2463-2464-2465-2466-2467-2468-2469-2470-2471-2472-2473-2474-2475-2476-2477-2478-2479-2480-2481-2482-2483-2484-2485-2486-2487-2488-2489-2490-2491-2492-2493-2494-2495-2496-2497-2498-2499-2500-2501-2502-2503-2504-2505-2506-2507-2508-2509-2510-2511-2512-2513-2514-2515-2516-2517-2518-2519-2520-2521-2522-2523-2524-2525-2526-2527-2528-2529-2530-2531-2532-2533-2534-2535-2536-2537-2538-2539-2540-2541-2542-2543-2544-2545-2546-2547-2548-2549-2550-2551-2552-2553-2554-2555-2556-2557-2558-2559-2560-2561-2562-2563-2564-2565-2566-2567-2568-2569-2570-2571-2572-2573-2574-2575-2576-2577-2578-2579-2580-2581-2582-2583-2584-2585-2586-2587-2588-2589-2590-2591-2592-2593-2594-2595-2596-2597-2598-2599-2600-2601-2602-2603-2604-2605-2606-2607-2608-2609-2610-2611-2612-2613-2614-2615-2616-2617-2618-2619-2620-2621-2622-2623-2624-2625-2626-2627-2628-2629-2630-2631-2632-2633-2634-2635-2636-2637-2638-2639-2640-2641-2642-2643-2644-2645-2646-2647-2648-2649-2650-2651-2652-2653-2654-2655-2656-2657-2658-2659-2660-2661-2662-2663-2664-2665-2666-2667-2668-2669-2670-2671-2672-2673-2674-2675-2676-2677-2678-2679-2680-2681-2682-2683-2684-2685-2686-2687-2688-2689-2690-2691-2692-2693-2694-2695-2696-2697-2698-2699-2700-2701-2702-2703-2704-2705-2706-2707-2708-2709-2710-2711-2712-2713-2714-2715-2716-2717-2718-2719-2720-2721-2722-2723-2724-2725-2726-2727-2728-2729-2730-2731-2732-2733-2734-2735-2736-2737-2738-2739-2740-2741-2742-2743-2744-2745-2746-2747-2748-2749-2750-2751-2752-2753-2754-2755-2756-2757-2758-2759-2760-2761-2762-2763-2764-2765-2766-2767-2768-2769-2770-2771-2772-2773-2774-2775-2776-2777-2778-2779-2780-2781-2782-2783-2784-2785-2786-2787-2788-2789-2790-2791-2792-2793-2794-2795-2796-2797-2798-2799-2800-2801-2802-2803-2804-2805-2806-2807-2808-2809-2810-2811-2812-2813-2814-2815-2816-2817-2818-2819-2820-2821-2822-2823-2824-2825-2826-2827-2828-2829-2830-2831-2832-2833-2834-2835-2836-2837-2838-2839-2840-2841-2842-2843-2844-2845-2846-2847-2848-2849-2850-2851-2852-2853-2854-2855-2856-2857-2858-2859-2860-2861-2862-2863-2864-2865-2866-2867-2868-2869-2870-2871-2872-2873-2874-2875-2876-2877-2878-2879-2880-2881-2882-2883-2884-2885-2886-2887-2888-2889-2890-2891-2892-2893-2894-2895-2896-2897-2898-2899-2900-2901-2902-2903-2904-2905-2906-2907-2908-2909-2910-2911-2912-2913-2914-2915-2916-2917-2918-2919-2920-2921-2922-2923-2924-2925-2926-2927-2928-2929-2930-2931-2932-2933-2934-2935-2936-2937-2938-2939-2940-2941-2942-2943-2944-2945-2946-2947-2948-2949-2950-2951-2952-2953-2954-2955-2956-2957-2958-2959-2960-2961-2962-2963-2964-2965-2966-2967-2968-2969-2970-2971-2972-2973-2974-2975-2976-2977-2978-2979-2980-2981-2982-2983-2984-2985-2986-2987-2988-2989-2990-2991-2992-2993-2994-2995-2996-2997-2998-2999-3000-3001-3002-3003-3004-3005-3006-3007-3008-3009-3010-3011-3012-3013-3014-3015-3016-3017-3018-3019-3020-3021-3022-3023-3024-3025-3026-3027-3028-3029-3030-3031-3032-3033-3034-3035-3036-3037-3038-3039-3040-3041-3042-3043-3044-3045-3046-3047-3048-3049-3050-3051-3052-3053-3054-3055-3056-3057-3058-3059-3060-3061-3062-3063-3064-3065-3066-3067-3068-3069-3070-3071-3072-3073-3074-3075-3076-3077-3078-3079-3080-3081-3082-3083-3084-3085-3086-3087-3088-3089-3090-3091-3092-3093-3094-3095-3096-3097-3098-3099-3100-3101-3102-3103-3104-3105-3106-3107-3108-3109-3110-3111-3112-3113-3114-3115-3116-3117-3118-3119-3120-3121-3122-3123-3124-3125-3126-3127-3128-3129-3130-3131-3132-3133-3134-3135-3136-3137-3138-3139-3140-3141-3142-3143-3144-3145-3146-3147-3148-3149-3150-3151-3152-3153-3154-3155-3156-3157-3158-3159-3160-3161-3162-3163-3164-3165-3166-3167-3168-3169-3170-3171-3172-3173-3174-3175-3176-3177-3178-3179-3180-3181-3182-3183-3184-3185-3186-3187-3188-3189-3190-3191-3192-3193-3194-3195-3196-3197-3198-3199-3200-3201-3202-3203-3204-3205-3206-3207-3208-3209-3210-3211-3212-3213-3214-3215-3216-3217-3218-3219-3220-3221-3222-3223-3224-3225-3226-3227-3228-3229-3230-3231-3232-3233-3234-3235-3236-3237-3238-3239-3240-3241-3242-3243-3244-3245-3246-3247-3248-3249-3250-3251-3252-3253-3254-3255-3256-3257-3258-3259-3260-3261-3262-3263-3264-3265-3266-3267-3268-3269-3270-3271-3272-3273-3274-3275-3276-3277-3278-3279-3280-3281-3282-3283-3284-3285-3286-3287-3288-3289-3290-3291-3292-3293-3294-3295-3296-3297-3298-3299-3300-3301-3302-3303-3304-3305-3306-3307-3308-3309-3310-3311-3312-3313-3314-3315-3316-3317-3318-3319-3320-3321-3322-3323-3324-3325-3326-3327-3328-3329-3330-3331-3332-3333-3334-3335-3336-3337-3338-3339-3340-3341-3342-3343-3344-3345-3346-3347-3348-3349-3350-3351-3352-3353-3354-3355-3356-3357-3358-3359-3360-3361-3362-3363-3364-3365-3366-3367-3368-3369-3370-3371-3372-3373-3374-3375-3376-3377-3378-3379-3380-3381-3382-3383-3384-3385-3386-3387-3388-3389-3390-3391-3392-3393-3394-3395-3396-3397-3398-3399-3400-3401-3402-3403-3404-3405-3406-3407-3408-3409-3410-3411-3412-3413-3414-3415-3416-3417-3418-3419-3420-3421-3422-3423-3424-3425-3426-3427-3428-3429-3430-3431-3432-3433-3434-3435-3436-3437-3438-3439-3440-3441-3442-3443-3444-3445-3446-3447-3448-3449-3450-3451-3452-3453-3454-3455-3456-3457-3458-3459-3460-3461-3462-3463-3464-3465-3466-3467-3468-3469-3470-3471-3472-3473-3474-3475-3476-3477-3478-3479-3480-3481-3482-3483-3484-3485-3486-3487-3488-3489-3490-3491-3492-3493-3494-3495-3496-3497-3498-3499-3500-3501-3502-3503-3504-3505-3506-3507-3508-3509-3510-3511-3512-3513-3514-3515-3516-3517-3518-3519-3520-3521-3522-3523-3524-3525-3526-3527-3528-3529-3530-3531-3532-3533-3534-3535-3536-3537-3538-3539-3540-3541-3542-3543-3544-3545-3546-3547-3548-3549-3550-3551-3552-3553-3554-3555-3556-3557-3558-3559-3560-3561-3562-3563-3564-3565-3566-3567-3568-3569-3570-3571-3572-3573-3574-3575-3576-3577-3578-3579-3580-3581-3582-3583-3584-3585-3586-3587-3588-3589-3590-3591-3592-3593-3594-3595-3596-3597-3598-3599-3600-3601-3602-3603-3604-3605-3606-3607-3608-3609-3610-3611-3612-3613-3614-3615-3616-3617-3618-3619-3620-3621-3622-3623-3624-3625-3626-3627-3628-3629-3630-3631-3632-3633-3634-3635-3636-3637-3638-3639-3640-3641-3642-3643-3644-3645-3646-3647-3648-3649-3650-3651-3652-3653-3654-3655-3656-3657-3658-3659-3660-3661-3662-3663-3664-3665-3666-3667-3668-3669-3670-3671-3672-3673-3674-3675-3676-3677-3678-3679-3680-3681-3682-3683-3684-3685-3686-3687-3688-3689-3690-3691-3692-3693-3694-3695-3696-3697-3698-3699-3700-3701-3702-3703-3704-3705-3706-3707-3708-3709-3710-3711-3712-3713-3714-3715-3716-3717-3718-3719-3720-3721-3722-3723-3724-3725-3726-3727-3728-3729-3730-3731-3732-3733-3734-3735-3736-3737-3738-3739-3740-3741-3742-3743-3744-3745-3746-3747-3748-3749-3750-3751-3752-3753-3754-3755-3756-3757-3758-3759-3760-3761-3762-3763-3764-3765-3766-3767-3768-3769-3770-3771-3772-3773-3774-3775-3776-3777-3778-3779-3780-3781-3782-3783-3784-3785-3786-3787-3788-3789-3790-3791-3792-3793-3794-3795-3796-3797-3798-3799-3800-3801-3802-3803-3804-3805-3806-3807-3808-3809-3810-3811-3812-3813-3814-3815-3816-3817-3818-3819-3820-3821-3822-3823-3824-3825-3826-3827-3828-3829-3830-3831-3832-3833-3834-3835-3836-3837-3838-3839-3840-3841-3842-3843-3844-3845-3846-3847-3848-3849-3850-3851-3852-3853-3854-3855-3856-3857-3858-3859-3860-3861-3862-3863-3864-3865-3866-3867-3868-3869-3870-3871-3872-3873-3874-3875-3876-3877-3878-3879-3880-3881-3882-3883-3884-3885-3886-3887-3888-3889-3890-3891-3892-3893-3894-3895-3896-3897-3898-3899-3900-3901-3902-3903-3904-3905-3906-3907-3908-3909-3910-3911-3912-3913-3914-3915-3916-3917-3918-3919-3920-3921-3922-3923-3924-3925-3926-3927-3928-3929-3930-3931-3932-3933-3934-3935-3936-3937-3938-3939-3940-3941-3942-3943-3944-3945-3946-3947-3948-3949-3950-3951-3952-3953-3954-3955-3956-3957-3958-3959-3960-3961-3962-3963-3964-3965-3966-3967-3968-3969-3970-3971-3972-3973-3974-3975-3976-3977-3978-3979-3980-3981-3982-3983-3984-3985-3986-3987-3988-3989-3990-3991-3992-3993-3994-3995-3996-3997-3998-3999-4000-4001-4002-4003-4004-4005-4006-4007-4008-4009-4010-4011-4012-4013-4014-4015-4016-4017-4018-4019-4020-4021-4022-4023-4024-4025-4026-4027-4028-4029-4030-4031-4032-4033-4034-4035-4036-4037-4038-4039-4040-4041-4042-4043-4044-4045-4046-4047-4048-4049-4050-4051-4052-4053-4054-4055-4056-4057-4058-4059-4060-4061-4062-4063-4064-4065-4066-4067-4068-4069-4070-4071-4072-4073-4074-4075-4076-4077-4078-4079-4080-4081-4082-4083-4084-4085-4086-4087-4088-4089-4090-4091-4092-4093-4094-4095-4096-4097-4098-4099-4100-4101-4102-4103-4104-4105-4106-4107-4108-4109-4110-4111-4112-4113-4114-4115-4116-4117-4118-4119-4120-4121-4122-4123-4124-4125-4126-4127-4128-4129-4130-4131-4132-4133-4134-4135-4136-4137-4138-4139-4140-4141-4142-4143-4144-4145-4146-4147-4148-4149-4150-4151-4152-4153-4154-4155-4156-4157-4158-4159-4160-4161-4162-4163-4164-4165-4166-4167-4168-4169-4170-4171-4172-4173-4174-4175-4176-4177-4178-4179-4180-4181-4182-4183-4184-4185-4186-4187-4188-4189-4190-4191-4192-4193-4194-4195-4196-4197-4198-4199-4200-4201-4202-4203-4204-4205-4206-4207-4208-4209-4210-4211-4212-4213-4214-4215-4216-4217-4218-4219-4220-4221-4222-4223-4224-4225-4226-4227-4228-4229-4230-4231-4232-4233-4234-4235-4236-4237-4238-4239-4240-4241-4242-4243-4244-4245-4246-4247-4248-4249-4250-4251-4252-4253-4254-4255-4256-4257-4258-4259-4260-4261-4262-4263-4264-4265-4266-4267-4268-4269-4270-4271-4272-4273-4274-4275-4276-4277-4278-4279-4280-4281-4282-4283-4284-4285-4286-4287-4288-4289-4290-4291-4292-4293-4294-4295-4296-4297-4298-4299-4300-4301-4302-4303-4304-4305-4306-4307-4308-4309-4310-4311-4312-4313-4314-4315-4316-4317-4318-4319-4320-4321-4322-4323-4324-4325-4326-4327-4328-4329-4330-4331-4332-4333-4334-4335-4336-4337-4338-4339-4340-4341-4342-4343-4344-4345-4346-4347-4348-4349-4350-4351-43